

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:
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PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY (PCT Rule 43bis.1)

Date of mailing (day/month/year) see form PCT/ISA/210 (second sheet)

Applicant's or agent's file reference see form PCT/ISA/220		FOR FURTHER ACTION See paragraph 2 below
International application No. PCT/IB2015/051988	International filing date (day/month/year) 18.03.2015	Priority date (day/month/year) 01.04.2014
International Patent Classification (IPC) or both national classification and IPC INV. C07D471/04 A61K31/4985 A61P25/28		
Applicant PFIZER INC.		

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☐ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step and industrial applicability; citations and explanations supporting such statement
- ☒ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☒ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1bis(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

Name and mailing address of the ISA:  European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Fax: +49 89 2399 - 4465	Date of completion of this opinion see form PCT/ISA/210	Authorized Officer Telephone No. +49 89 2399-0 
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Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of:
 - ☒ the international application in the language in which it was filed.
 - ☐ a translation of the international application into , which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1 (b)).
2. ☐ This opinion has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 43bis.1(a))
3. ☐ With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, this opinion has been established on the basis of a sequence listing:
 - a. ☐ forming part of the international application as filed:
 - ☐ in the form of an Annex C/ST.25 text file.
 - ☐ on paper or in the form of an image file.
 - b. ☐ furnished together with the international application under PCT Rule 13ter.1(a) for the purposes of international search only in the form of an Annex C/ST.25 text file.
 - c. ☐ furnished subsequent to the international filing date for the purposes of international search only:
 - ☐ in the form of an Annex C/ST.25 text file (Rule 13ter.1(a)).
 - ☐ on paper or in the form of an image file (Rule 13ter.1(b) and Administrative Instructions, Section 713).
4. ☐ In addition, in the case that more than one version or copy of a sequence listing has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that forming part of the application as filed or does not go beyond the application as filed, as appropriate, were furnished.
5. Additional comments:

Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes: Claims	<u>11-22</u>
	No: Claims	<u>1-10</u>
Inventive step (IS)	Yes: Claims	
	No: Claims	<u>1-22</u>
Industrial applicability (IA)	Yes: Claims	<u>1-22</u>
	No: Claims	

2. Citations and explanations

see separate sheet

Box No. VI Certain documents cited

1. Certain published documents (Rules 43bis.1 and 70.10)

and / or

2. Non-written disclosures (Rules 43bis.1 and 70.9)

see form 210

Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Claims 20 and 22 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 39.1(iv)/ 67.1(iv) PCT. The patentability can be dependent upon the formulation of the claims. The EPO, for example, does not recognize as patentable claims to the use of a compound in medical treatment, but may allow claims to a known compound for first or further medical treatment.

2. Reference is made to the following documents:

- D1 WO 2013/171712 A1 (JANSSEN PHARMACEUTICALS INC [US]) 21 November 2013 (2013-11-21)
- D2 MARTIN PETTERSSON ET AL: "Design, Synthesis, and Pharmacological Evaluation of a Novel Series of Pyridopyrazine-1,6-dione [gamma]-Secretase Modulators", JOURNAL OF MEDICINAL CHEMISTRY, vol. 57, no. 3, 13 February 2014, pages 1046-1062, XP055156862
- D3 US 2012/252758 A1 (PETTERSSON MARTIN YOUNGJIN [US] ET AL) 4 October 2012, cited in the application
- D4 US 2014/088111 A1 (PETTERSSON MARTIN YOUNGJIN [US] ET AL) 27 March 2014

3. The present application is directed to 3,4-dihydro-2H-pyrido[1,2-a]pirazine-1,6-dione as gamma-secretase modulators for the treatment of neurodegenerative disorders such as Alzheimer.

D1-D4 are all related to the same technical field.

The claimed compounds differ from the gamma-secretase modulators of D2 and D4 on account of the ring A.

The gamma-secretase modulators of D3 differ from those claimed on account of the -O-R3 substituent.

There is an overlap between the compounds of current claim 1 wherein A=A3 and claim 1 of D1 when Ar is chosen as 1,2,3,4-tetrahydro-1-naphthalenyl and indanyl in claim 1 of D1. Although D1 does not disclose specific compounds in the overlapping area, there is no apparent new technical (structural) teaching which distinguishes the subject matter claimed from the prior art in the sense of a novel selection.

An objection of lack of novelty under Article 33(2) PCT over D1 consequently arises for the subject-matter of claims 1-10.

4. The present opinion on inventive step concerns the subject-matter which satisfies the requirements for novelty (claims 11-18, and claims 19-22 as far as they are dependent on claims 11-18):

The present application is directed to 3,4-dihydro-2H-pyrido[1,2-a]pirazine-1,6-dione as gamma-secretase modulators for the treatment of neurodegenerative disorders such as Alzheimer.

D1 is considered to be the closest prior art document.

The compounds of current claims 11-18 differ from the gamma-secretase modulators of D1 on account of the ring A, which is a chromene based substituent.

As this difference does not result in any additional effect, the objective technical problem to be solved by the present application may be seen in the provision of compounds as gamma-secretase inhibitors useful for the treatment of neurodegenerative disorders.

The skilled person would be prompted to change the substituent R1 of the compounds of D1 since the compounds of D2-D4 have several different heterocycle at this position. Thus, the replacement of the listed heterocycle Ar in claim 1 of D1 with a chromene based moiety is merely one of several straightforward possibilities from which the skilled person would select, in accordance with circumstances, without the exercise of inventive skill, in order to solve the problem posed.

The claimed compounds are considered to be obvious alternatives of the compounds of D1.

Consequently the technical problem to be solved by the present application must be reformulated as the provision of compounds as gamma secretase modulators which exhibit an unexpected technical effect over the compounds of D1.

The present application does not contain any evidence as regards to such surprising effect over D1, for example, comparative data between a representative set of compounds of the present application and the compounds of the prior art presenting maximal structural similarity to show convincingly that the unexpected effect indeed has its origin in the distinguishing feature, ie the chromene base substituent A.

Furthermore, it should also be credible that this surprising effect occurs over the whole range claimed: all the current illustrative examples in the description have a 4-methyl-1H-imidazolyl group as R1-X- and "y" is always 1 whereas in claim 1 X is claimed to be a 5-14 membered heteroaryl containing 1-3 heteroatoms and "y" can vary from 1 to 4. Thus, claim 1 cannot be considered to be a reasonable generalisation of the examples of the description and it does therefore not appear credible that substantially all claimed compounds would provide a surprising technical effect over D1.

For the time being and in the absence of evidence for an unexpected technical effect of a representative set of claimed compounds over D1, Article 33(3) PCT in conjunction with Articles 5 and 6 PCT cannot be considered to be satisfied.

Re Item VI

Certain documents cited

Application No Patent No	Publication date (day/month/year)	Filing date (day/month/year)	Priority date (<i>valid claim</i>) (day/month/year)
WO2014111457	24.07.2014	16.01.2014	17.01.2013
WO2015049616	09.04.2015	22.09.2014	04.10.2013

These intermediate documents are not taken into account in this written opinion according to the Chap II PCT proceedings. It should nevertheless be noticed that the extensive examination of these documents, on the question whether they constitute prior art or not, will depend essentially on the analysis of the claimed priority rights of the present application and will only be performed in the regional European proceedings to come.

Re Item VIII

Certain observations on the international application

There is a discrepancy between the description and the claims since it is stated on p. 17 of the description that prodrugs and compounds containing protective groups are also included within the claimed scope.

Contrary to the requirements of Rule 5.1(a)(ii) PCT, the relevant background art disclosed in D1 is not mentioned in the description, nor is this document identified therein.